Synthesis of nanoscale carceplexes from deep-cavity cavitands†

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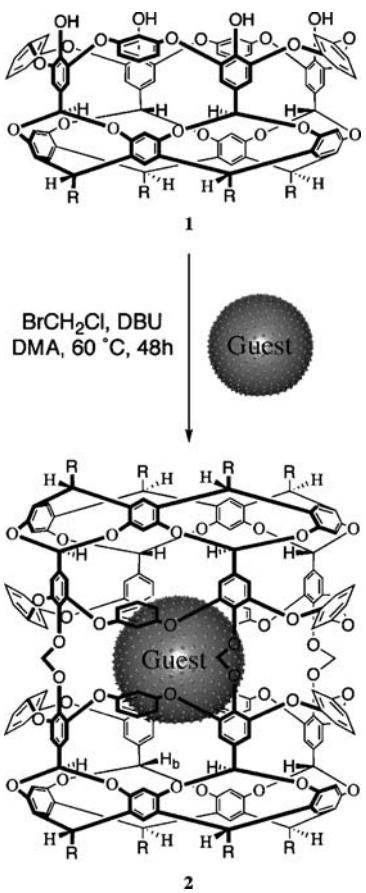
Deep-cavity cavitands were shown to undergo carceplex reactions in which two cavitand tetrols were covalently linked using bromochloromethane; the efficiency of the "dimerization" was closely tied to the templating guest molecule incarcerated within the host.

The formation of carceplexes and hemicarceplexes[1–3]—complexes in which a shell-like carcerand or hemicarcerand completely envelops a guest molecule within its enforced hollow interior—has revealed considerable information pertaining to the templation of kinetically controlled assemblies.[4–9] In addition, the covalent nature of these container molecules makes them ideal for the study of highly reactive species such as cyclobutadiene[10] and *o*-benzyne,[11] and more generally, makes them excellent nanoscale reactors.[12,13] With these ideas in mind, there are three ways that (hemi)carcerands can be increased in size. One option is to lengthen the linking moieties between the cavitand subunits. The resulting hemicarceplexes[1–3] have been utilized to great effect by Warmuth *et al.*, in the study of highly reactive carbenes, nitrenes and their ilk.[14–19] A second, more recently developed approach to larger carcerands is to assemble the target using not two cavitands, but three[20] or even six such subunits.[21–24] Here we demonstrate that the third option, namely using larger cavitands, is also a practical approach to carceplex synthesis.

Previously, we have reported on the synthesis of a family of deep-cavity cavitands typified by **1** (Scheme 1). The core, twelve-ring, structure of these hosts is built up in three steps from the base resorcinarene;[25–28] whilst functionalization of the rim or concave surface of these hosts can be brought about by either electrophilic attack[29] or directed *ortho*-metalation processes.[30,31] Thus, tetraphenol **1** (R = CH_2CH_2Ph) can be synthesized in 40–50% yield by treating the corresponding unsubstituted cavitand with excess *sec*-BuLi, quenching with $B(OMe)_3$, and oxidative work-up with H_2O_2–NaOH.[31]

We first investigated carceplex (**guest@2**) formation in the absence of any large templating guest. When cavitand **1** was treated with excess DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and $BrCH_2Cl$ in DMA (dimethyl acetamide), no discernable product was formed; instead, only polymeric material was evident. We had previously shown that similarly sized supramolecular capsules that assemble *via* the hydrophobic effect were strong binders of steroids[32] and molecules of that size.[33–35] Thus, we subsequently turned to steroids to evaluate their ability to template carceplex formation. When the above reaction was repeated in the presence of (+)-dehydroisoandrosterone **3** (Fig. 1), the corresponding C_1 symmetric carceplex was isolated in 5% yield (average of four runs, σ = 2.8). As anticipated, the guest signals in this carceplex were shifted considerably upfield from those of the corresponding free steroid (Fig. 2). The highest field signal (*ca.* −3.01 ppm) corresponded to the C-3 hydroxy group, indicating that it resides deep in the 'polar' region of the carcerand. Of the two methyl groups, the C-18 methyl underwent the greater shift, presumably because the 5-membered D-ring of the steroid can bind more deeply than the 6-membered A-ring. Regarding the host region of the NMR spectrum, the anisotropic nature of the two hemispheres was evident in considerable signal splitting; in particular the inward pointing benzal protons (*ca.* 4.30



Scheme 1 The synthesis of nanoscale carceplex **guest@2** (R = CH_2CH_2Ph).

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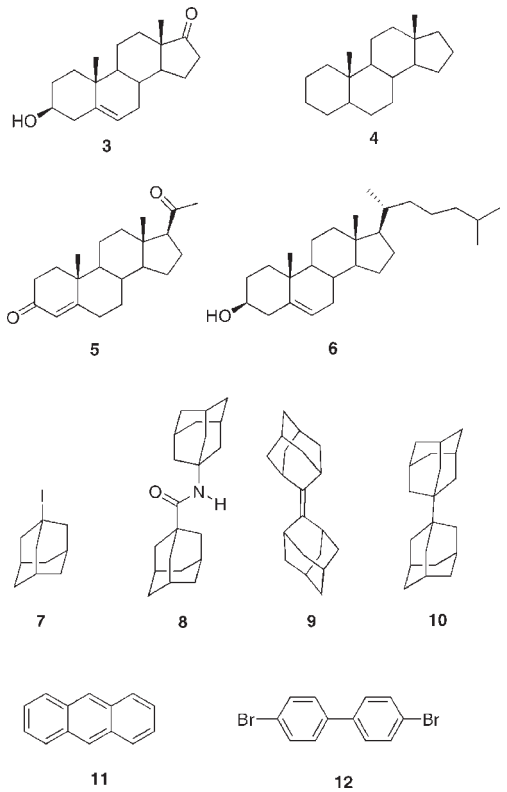

Fig. 1 Guests examined for their templation properties.

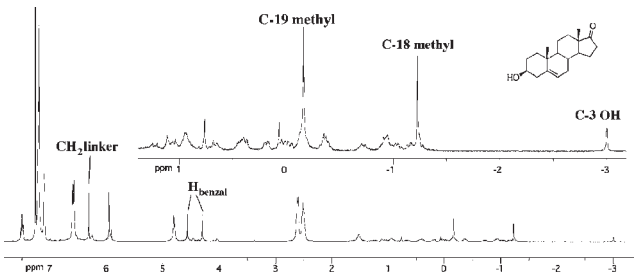

Fig. 2 NMR spectrum of carceplex **3**@**2**.

and 4.56 ppm, H_b in Scheme 1), whilst the new linker group between the hemispheres was evident at *ca*. 6.32 ppm.

We subsequently probed the general ability of steroids to template carceplex formation with smaller and less polar 5α-androstane **4**, the slightly larger and more polar progesterone **5**, and the considerably larger cholesterol **6**. 5α-Androstane **4** proved to be a better template, giving a 9% yield of the corresponding carceplex (average of three runs, $\sigma = 1.1$). In contrast, only a 2% yield of **5**@**2** could be isolated (average of two runs, $\sigma = 0.15$), and no carceplex could be recovered with cholesterol **6**. Evidently, **5** is at the size limit of carceplex formation, whilst **6** is too large. Carceplexes **3**@**2** and **4**@**2** possessed very limited solubility in most organic solvents, and consequently it was not possible to perform NOESY NMR analyses of these complexes. However, the carceplex **5**@**2** did possess sufficient solubility for this purpose. Evident in the spectrum were through-space interactions between the benzal hydrogens (H_b) of the host and the C-4 vinyl proton, C-16 methylene protons and C-21 methyl protons of the steroid. No through-space interactions were evident between the host and the C-18 or C-19 methyls of the guest.

Adamantane derivatives have proven to be some of the best guests for deep-cavity cavitands, and so carceplex formation with iodoadamantane **7**, amide **8**, adamantylidene-adamantane **9**, and 1,1′-diadamantyl **10** were also investigated. Of all the guests we have observed binding to deep-cavity cavitands, 1-iodoadamantane **7** binds the strongest ($K_a = 1.4 \times 10^5$ M^{-1} in DMSO-d_6).[36] Thus, although the possibility of hydrolysis or alkylation of free guest could complicate matters, we sought to ascertain whether one or two copies of **7** could be trapped within the carcerand. Surprisingly, no carceplex was observed with **7**, nor indeed when **8** was added to the reaction. In contrast, guests **9** and in particular, **10**, were successful templates. The former, essentially a hydrocarbon cylinder 9.99 × 4.39 Å, gave the corresponding carceplex in 5% yield (average of two runs, $\sigma = 1.4$), whilst the latter, a slightly shorter 9.33 × 4.41 Å hydrocarbon cylinder, resulted in a 38% yield (average of two runs, $\sigma = 1.4$) of carceplex. In other words, guest **10** is capable of inducing average yields of 89% for the eight bonds that are formed in the reaction.

Good templates in carceplex reactions are complementary with the transition state leading to guest entrapment (the bis-bridged species).[7] Apparently, this transition state leading to **guest**@**2** readily differentiates between molecules that differ in weight, surface area, and volume, by only 2 amu, 2.5 $Å^2$ and 3.9 $Å^3$, respectively. In contrast, longer and less rotund guests such as steroids cannot form so many noncovalent interactions with the forming host, and inhibit somewhat the approach of one cavitand to the next. However, they are still better templates than guests that are on the small side; with smaller guest **7**, as well as with others that our experience with water-soluble capsules[32–35] suggest would form complexes, (*e.g*., anthracene **11** and 4,4′-dibromobiphenyl **12**), no assembly was observed. If small molecules prove unsuitable for templating irreversible assemblies of hosts with large cavities, it may be difficult to ascertain the 'ultimate' template for these processes, as families of large, structurally complex homologues cannot usually be taken ''off-the-shelf.''

In conclusion, we have demonstrated that large molecules such as steroids and diadamantanes can template the formation of nanoscale carceplexes from deep-cavity cavitands. Further studies are underway to determine the range of compounds that can promote this templation process, and potentially identify guests that are better templates than diadamantyl **10**.

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